TODAY'S NEUROSCIENCE, TOMORROW'S HISTORY

A Video Archive Project

Professor Richard Frackowiak

Interviewed by Richard Thomas

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Interview transcript

Schooldays in London

My parents were immigrants, of course, after the war. We spoke Polish at home because that community thought they were there, you know. Communism was a passing phase. They were absolutely right but they just got the time course a bit long, but the advantage was that we got an extra culture, an extra language - structured differently. It's a very regular language, based on Latin - unlike English, which is of course a very irregular language. Well, then it was secondary school, and you know, the Poles are quite Catholic, you know. John Paul II had forty million cousins, you know that. But the best school in the surroundings was Latymer Upper. Well, there was St. Paul's a little further along, but the rivalry was already there - you didn't need league tables. And so there, at the time, they were direct grant schools, so there were scholarships. So, I got a scholarship into grammar school, and then just went through Latymer.

My first love at school - intellectual love at school - was history, and the philosophy club, but then I got hooked on biology, specifically, and quite liked chemistry, but *detested* physics because there was too much mathematics and I'm, you know, not a very mathematical person in terms of the mechanics of it, though I can grab the concepts. And so that was the sort of navigation through the waters, and I took - I think it was - yes, chemistry, biology, physics. Got my grades - did quite well in biology nationally.**)**

Early influences and Cambridge University

Throughout my time at Cambridge, I became more and more interested in the neurological side of things. I sometimes think it had something to do with my philosophical bent when I was a kid, but I certainly remember an individual who influenced me, and this was a strange,

lonely bachelor, who was the local GP in Chiswick, who was Polish, and who would come to my family home almost every day for about ten years, sit at table and natter to my father, while my mother fed him. And he went through some extraordinary experiences during the Warsaw uprising, you know - surgery on tabletops without anaesthesia - all this sort of stuff, and yet was totally devoted to the local community and an excellent diagnostician. So, our local greengrocer always gave him his vegetables because he walked in one day and said, 'Get that child into hospital' - and it was the beginnings of Polio and the child did very well. You know, that sort of thing. So that was terribly impressive for a youngster.

Hammersmith Hospital and a meeting with Professor Terry Jones, 1979

So, I got through my general medicine pretty quickly and was oriented towards neurology, and had an extremely, extremely wise, even though quite young, and highly energetic mentor at the time, who, when he knew I was getting ready to go on to the further phases of my career, said, 'So, are you still interested in research?' And I said, 'Yes.' 'And so, what would you like to do?' I said, 'Well, you know, I'm interested in neuroscience and neurology.' And he said, 'Well, go along and see this chap, Terry Jones, in the MRC Cyclotron Unit.' I said, 'Okay, but what does he do?' He said, 'He's got some sort of machine that looks at the brain.' 'Fine,' I said. 'I'll go and have a look.' 'And come back after lunch and tell me if you're going to do it or not.'

So again, it was one of those decisions made on the spot, which completely changed my life, because I met Terry, who *really* didn't trust me at all. There was a very nice fellow from Italy there called Gian-Luigi Lenzi, who has become a dear, dear friend and is Professor of Neurology at Rome now, who also really resented me coming along because he and Terry had, you know, formed a good, tight group and they were beginning to use Oxygen-15 on these positron emission traces, and Terry had just managed to convince the MRC to give them money to get a positron emission tomograph, or a camera, as I used to call it. And here was this upstart turning up, who'd done neurology for a year at the Hammersmith and never bothered to go and see them. So, I sort of understood why they might be a little resentful at being foisted on with this fellow. That was 1979, and so I got stuck in, and the first thing I did was … I mean, I was delighted because this was the first machine of its type, and it was only a year after the French had put a machine in, and only, probably, a couple of years after the Americans had started work with Phelps and Raichle over in St Louis - and subsequently, Los Angeles for Phelps. And I had to get stuck into the, you know, the physiology of the brain, and it was absolutely fascinating. There was a story that started off as Seymour Kety in the war, and then in '48 a magnificent paper about blood flow and how you could measure it in the human brain. They were talking non-invasive then, but they were sticking needles

into arteries - carotid arteries - and jugular veins, and measuring arterial-venous oxygen differences, and extractions of oxygen as the blood flowed through the cerebral capillaries and out again into the venous side, and relating that to blood flow.

Then the *annus mirabulus* of our whole discipline – 1973 - Hounsfield, of course - the first CT scanner in London. The first one was down in St Georges, and then the second one very quickly afterwards at Queen Square, and I began to use that as a young house officer, a young doctor. And was learning anatomy, on the one hand, from these blurred images of the human brain, and on the other hand, spending the night with Brian Kendall, who was the neuro-radiologist at the time - stuffing needles into people's carotids, and then pulling back a bit to get into the superior vena cava, injecting dyes in order to diagnose horrible tumours in their brains. I mean, all that disappeared almost, almost overnight. It was a wonderful, wonderful time *but* the principle it established - of being able to examine the distribution of the density or the activity in the brain - quickly, very quickly, was understood by Phelps, by Ter-Pogossian and then – bang! – away they went and started creating the first PET scanners -Ter-Pogossian particularly - putting them all together. And Terry Jones, who was there at the time, realised this was going to be a very big thing and came back and fought like hell to get something - getting lots of good preliminary data with gamma cameras and things like that. And - bang! - the machine arrived on 1st July 1979 and I arrived on 1st August 1979, so it was a concatenation of events, which just put me in a place at a time. People aren't ever as lucky as that more than once in a lifetime.

PET (positron emission tomography) – devising methods for visualising brain energetics

Terry Jones, who was my mentor, understood that the very short-lived isotopes were extremely useful. Firstly, because you could have them come into the brain and be washed out of the brain, but because of their short half-life they also decayed from the brain, so you could set up steady states where what was coming in and what was leaving out into the veins and as radioactive decay, established an equilibrium. And that equilibrium was dependent on the input, and the input was, of course, cerebral blood flow. And if you could do that regionally, you could look at the regional amount of cerebral blood flow, and because neural activity was linked to local perfusion - local cerebral blood flow, essentially - told you what neural activity there was. And the second advantage of oxygen-15 was that it was an isotope of the atom that was actually there, so it would not be changing anything going on in the brain.

So, Larsen and Ingvar had done all the previous work on very long-lived isotopes, but what they were battling against was the inability to actually measure the amount of isotope locally in the brain. So, what the whole … the whole era of tomography brought was the ability to measure locally in the brain, and then what positron tomography brought was, because of the way these positron emitters decayed sending out two photons, which were detected on either side by two receptors, which were simultaneously detecting - so you could isolate where the thing came from - you could also correct for the attenuation of these photons as they went through the tissue and get an absolute value of the concentration of the isotope in each part of the brain. Now, that then allowed you to transform that into an absolute measure of cerebral blood flow - mLs per hundred mLs of brain per minute - and that quantitation is still by far and away the greatest advantage of positron tomography. Now, when we were interested in looking at brain energetics, there's blood flow, there's oxygen consumption, and there was glucose consumption. Those were the three issues.

Oxygen-15 allowed us to make measures in five minutes, initially - a bit shorter later on. Raichle developed a very rapid technique where there were certain other assumptions involved, which we might talk about later, but they allowed repetitions because the amount of radioactivity given per shot was much less than with the Flourine-18 FDG. And so you could do up to six, perhaps even twelve, repetitions, so that gave you a sort of dynamic perspective. And oxygen consumption – well, that came from the fractional oxygen extraction, which involved breathing oxygen instead of breathing carbon dioxide or injecting it as an isotope labelled with oxygen-15. And that was … that was really common to everyone. So, those were the three things that we had available, and people tailored questions and methods of measurement to each other. Those various techniques evolved over the early eighties.

PET – pioneers in the field

I think the first period was intensely competitive. We and the Europeans decided to invest hard in single units in each country, so France invested in Orsay where Jean Claude Baron, was the sort of equivalent of myself - we were very close in age. We were like brothers so to speak, in arms at that time. There's me and Terry and Gian-Luigi in London. The Americans - so Phelps left St Louis and went off to Los Angeles with a young man who was also deeply committed to anatomy of the brain and to its function. That was John Mazziotta, who also, after that first initial period of intense competition became a very close friend. We were very cheeky in those days. When I first met Mike Phelps – I have no compunction about telling this story because he tells it so frequently himself – it's one of many stories, actually. I was walking down the corridor - *big* international meeting in St Louis - with Terry, and there was

this chap walking the other way - boyish face - bouncing along with a couple of people around him. Terry stopped me and said, ‘Hi Mike. How are you? I’d like you to meet Richard Frackowiak.’ And I looked at Terry, and I looked at this sort of boyish fellow who was 5’6’’, or perhaps slightly taller, and Terry said, ‘Well, what do you think?’ And I said, ‘Well, I thought he’d be older and taller.’ And Mike was really amused by this, but at the same time, I think there was an element of ‘Who *is* this?’ [laughs] So on we went, and we began to develop relationships across the Atlantic.

Recruiting a team at the MRC Cyclotron Unit

What I wanted to do was to get away from pathophysiology of brain disease -we’d been studying Alzheimer’s and ageing and stuff. I wanted really to understand the structure and functional architecture of the human brain in normals first, because I was coming up intellectually against a barrier. I didn’t understand enough about the normal to be able to interpret what was happening in pathology properly, and so we started recruiting. And so Karl Friston, who was … had been on psychiatry rotation – he was going to be a psychiatrist – but he’d done a year of quantum physics at Cambridge so he knew about statistics. Maria Ron, who was the professor of Neuropsychiatry at the National, brought a young man called Ray Dolan along, a registrar, and Ray was full of ideas about emotion and cognition, and emotion and memory. And so I got him engaged in a big way and he started working with us. Chris Frith. Someone from the high echelons of the MRC, said to me, ‘There’s this guy who’s really experienced. He’s out at Northwick Park. They’re closing down Northwick Park. He’s very interesting in schizophrenia; he’s done some imaging work’ - pretty basic by today’s standards. And I met Chris, and Chris was very interested, and actually, you couldn’t recruit him, he was already an established scientist - MRC scientist. So, it was a question of wooing him. It took four years to woo him. Also one or two of my clinical colleagues - there was Richard Wise, David Brooks - who were pushing up from the ranks of registrars and senior registrars, and who really knew what they were doing, and we got them involved.

PET - normal brain function and the concept of redundancy networks

In our work in the Cyclotron Unit, particularly in the phase after the delivery of the machine, which gave us coverage of the whole brain, we suddenly were able to look at normal brain function, which was the great dream. And Raichle had already shown us the way with his techniques, and so away we went, injecting water as Raichle had shown, and just measuring cerebral blood flow, and not getting involved in the oxygen consumption. And we were able to address very basic things, so this is where my collaboration with Semir Zeki was so important because Semir, of course, had done a lot of very fundamental anatomical work in primates, bringing out this idea of parallel processing, functional specialised pre-striate

areas, and so on. And it became perfectly clear to me that one outstanding validation of all of this would be to show something equivalent in the human, and of course, Semir was interested in it from the point of view of how that then impacted on all his interests in higher visual perception and visual consciousness, and so on. So, we had a very fruitful time with some common fellows - John Watson was a very important one, Christian Lueck - and that first paper on visual colour, with Mondrians - visual motion - then things on patients who had problems with seeing visual motion, on blind sight – a whole series of papers came out over the next four or five years, most of them with PET - all of them with PET initially.

I mean, there's this famous patient with blind sight that Larry and others had examined, and that Semir was examining at the time, psychophysically. This was a man who could not see in one visual field, and if I remember correctly, it was to the right of the vertical, though he occasionally said that he had a sort of an impression that there might be some dim something or other going on there, but really, he was blind. And yet he could make judgments as to whether there was something moving in that field or not, when asked to do so, simply as a guess. And so, he would get up to sixty per cent - seventy per cent – eighty per cent correct, rather than fifty per cent random, if you forced choices between 'there is' and 'there isn't'. And the interesting thing was that when we imaged him - and I think this was a very major insight of Semir's, and related to his anatomical knowledge - because I was a bit sceptical about imaging people who had lost a function. It seemed to me, if you lose a function, why image them because you won't see anything, but in fact, in this particular instance, you got activation of the visual motion areas V5, and Semir's knowledge of anatomy indicated that that might be because of direct pathways from lower areas straight to V5 rather than passing through V1 in the classical way. And then we did some electrophysiological studies with colleagues in Germany to show that, actually, you could detect electrically evoked potentials in these areas before you detected the main volley coming into the primary visual cortex. So, it made a very nice story of new pathways, or minor pathways, which might become involved under certain circumstances, and that had major implications for our concept of redundancy networks - major implications three-four years on in terms of how functions recover when you knock out large areas. How other components of the brain, which *are* connected but are not usually used in order to subtend a particular function, suddenly become engaged and interact and bring about that function to a greater or lesser extent.

PET - Statitistical Parametric Mapping (SPM)

In science, essentially, what you do is you can scope the territory but then you'd have to generate hypotheses, and in order to answer those hypotheses, you need to sample the

populations you're interested in, take the measurements, compare them, and then draw your inferences. So you need populations - you need representative populations, right, or representative samples of populations. So, that the whole issue was - the first big issue was - how to get brains of different size and shape into a standard space, and then there were initial, sort of quite crude … but the preliminary attempts were done by Fox in Raichle's lab, and then he went on and did some more stuff down in San Antonio on his own. He came over to us when we started to do all these strange new ways of warping brains and so on, and that whole thing took from about '88 through to about '94.

Then there was the statistics, so the initial V5 paper that I did with Semir and with others - Christian Lueck and others - which Karl was involved in, the statistics were quite simple statistics, and the thresholds were just beginning to, sort of, get an idea of how one might have to go about that. And then over, it took up to '92, '91 - '92, '93, '94 again - Karl working with Worsley in McGill, who was a *bona fide* statistician, who really got that together. And then, as soon as the thresholds and the warping was done, then it was simply a question of bringing, you know, from univariate to multivariate … bringing in all the different categorical … going from categorical comparisons to parametric designs, and then the biggest jump - which was about '95 - which was this whole notion of looking at non-linear interactions between brain regions, going to the factorial designs and so on. So, it was very much a strategy. It was a strategy that took a number of years, a number of key papers, which are now very highly cited. Building this SPM framework, it's become a worldwide network. There are more than three thousand labs using it. There's a helpline with thousands of questions and answers being answered by different people in the network worldwide. People produce new routines which are of use - they get incorporated. We've just had the SPM homecoming. We have an annual homecoming here where Karl gets his people together and they come from the whole world.

MRI (Magnetic Resonance Imaging) - a new Imaging Centre, Queen Square, 1995

So, the group grew organically up to about 1992 and the MRC came and reviewed us and gave us an A-star, or whatever they were called in those days, I can't remember - the equivalent of a programme - but said, 'No, you can't have an MRI machine. You'll have to use time on the one in the hospital.' And there was this sort of lack of comprehension that this was the next big push coming out of PET into function of the brain - was going to be through MRI. And so we started … I started looking around - where to go. There was America, where all sorts of interesting things were happening. And I met David Gordon who was deputy secretary, I think, of the Wellcome Trust at the time – perhaps he wasn't called a secretary, he was called something like that - Deputy Director. And he … we were having a

chat in a queue in an Oxford college going into an Alzheimer's disease symposium, and he said, 'Why don't you apply for a programme grant at the Wellcome?' I'd been banging on about not getting an MRI machine. I said, 'Don't be silly. This would be – off the top of my head - £20 million.' He said, 'Why don't you apply for a programme grant then?' 'David, you didn't hear me.' 'Why don't you apply…' I said, 'I hear you.' So, I went away and wrote the grant.

The Trust had very few administrators at the time and was flush, flush with cash. We were so lucky, we got all the money; we could do what we liked with it. There was no one, no one to control it, so we designed and built the building essentially ourselves. We designed our governance so it's always been a flat governance with a principals' meetings, everything being decided there, nothing outside, nothing in the corridors and so on. And creating that ethos was absolutely critical to the success of the place. And the other principles we had, right early on, was as many women as men, as many foreigners as indigenous, no-one sitting next to anyone else who is of the same discipline, no-one sitting next to anyone else working on the same project, open-plan labs. Principals seen by the fellows to be working together, not combating each other. The fight was with the outside world, and not inside, and that has pretty much continued. There's been a lot of pressure put on to try and identify who was responsible for what, specifically. 'What did you do? What did you do?' Absolute lack of comprehension of the whole dynamic of this sort of big science, but I think a lot of the things we did very early on have become part and parcel of normal scientific life. I mean, you know, away-days and retreats, and this sort of stuff.

One thing I should say is that there was one person who was absolutely critical to, I think, the overview and the actual enabling of this whole extraordinary event, which was the setting up of the Functional Imaging Laboratory, which we called the FIL. It's known the world over as the FIL. It's now the Wellcome Trust Centre for Neuroimaging, but it's still the FIL. So, the person who I'd really need to mention is Sir Stanley Peart. Stan Peart was for magnetic resonance. He had worked a lot with David Gadian and seen what was possible. He was very close to Semir Zeki and to David Gordon. They went and educated themselves. They went around centres left, right and centre, and it was their backing, really, of a political type, and of an institutional type, which was absolutely critical to getting the money, because it was actually quite unprecedented - £20 million in one go.

BOLD (Blood Oxygen Level Dependent) MRI – a new non-invasive imaging technique

Ogawa's great contribution was that he was able to show that by the deoxygenation of blood through neural activity would lead to a local change in magnetic signal that could be picked

up, and he called that the blood oxygen level dependence signal and he started examining that because it became clear after that, that part of the change in signal was also probably due to a small change in local volume, quite apart from the change in the oxy-deoxyhaemoglobin ratio. There may even have been change in signal due to local water swelling or changes in cell water content and such like, and that's led us to a slightly curious situation where we were moving for a technique that was completely quantifiable, in absolute terms – callibratable - to a situation where we now had a signal that we didn't completely understand the underlying physiology of. And so the whole issue now was to try and validate that signal in physiological terms, and in terms of what PET had told us before, which is one of the main strategic reasons why I thought we should have PET and MR here. But in that first five years it was very clear that that was absolutely the right assumption, absolutely the right thing, and we dropped PET and we got another MR camera in '99.

PET was finished, and we were now into the BOLD era, and we were into an area of relative change so we were able to follow relative changes across time - relative changes from either some baseline condition, or rest condition, or default condition, or whatever you like to call it, and a condition of interest - relative changes as a function of a parameter that changed, relative changes that occurred when two factors or more interacted with each other. And this became an extremely rich signal, but one which we still tried to get information about in terms of its basic underlying, physiological mechanism, and I suppose the piece of evidence that's been most important has been that of Logothetis who has been able to show in monkeys that the local change in bowl signal correlates best with what's called the local field potential, which means the aggregated activity of all the synapses in an area.

Bringing together brain structure and function

Okay, so BOLD is definitely functional MRI, but in about 1996 – '95, '96, '97 – somewhere around there, it became clear to us that SPM used for the analysis of functional imaging in general, was really just a mathematical analysis of a block of scanned data, and a structural image was also a block of scanned data, so why not apply exactly the same techniques to the structural images, rather than functional images? And lo and behold – bingo! - I mean, the sensitivity for detection of diffuse, small changes in the local concentration of grey matter or white matter in the human brain regionally, became a reality, and not only was that important, but much more important was the fact that you then, within the same framework of data capture, and the same framework of data analysis, were able to bring structure and function together in a very sensitive manner.

The methodological agenda was no longer a group agenda, it was Karl's agenda, and Karl was now driving that. So, from '94 really, he's the sole person, and prior to that, all sorts of interesting things. I remember, one of the first breakthroughs was Ray Dolan coming into the big lab with an old book – it must have been 1930 or 1940 – a little pamphlet on ANCOVA, dropping it on Karl's desk and saying, 'What do you think of that?' You know, four or five weeks later, out came this this wonderful way of beginning to analyse the results. So, that whole methodological thing, I took a big role in the political side of that. Political. By political, I meant …I talked to you about the brickbats, about whether this was a science or not, and it became very clear to me that the idea had to be a quantitative science. If we couldn't get the same results in different laboratories, or analyse the same data and get the same result, then there was just, there was no point. And so, I was determined, and very single-minded – some people still blame me for having been quite so single-minded – of trying to get across the generic methods of analysis which were packaged in the thing we call SPM, in the lab. But where - it wasn't that it was SPM - what I wanted everyone to start doing is getting involved in the generic, analytical techniques using standard statistics applied to large image data sets, and that, by the way, was a much better way of bringing together all the data - which others have tried to do by databasing results - than any databasing. And the fact that now we do have a science, and now there are people with different implementations of these techniques, but they are, they have one set, and they're principled, and they've been validated and so on. Personally, I think its one of my greatest achievements.

The secret of a great laboratory

Essentially, someone has to be broad in these areas, in this sort of science where you go from methodology all the way, to applications or to deep understanding of basic mechanisms. I'd done quite a lot of sort of in-depth stuff in the '80s with PET, but even there, things had begun to spread and to widen, and certainly, between '88 and '94, I had to get really broad and really think about the future. Now we have the Centre, everything's you know, highly cited. You know, four of our PIs, but including me, amongst the most highly cited in neuroscience in the whole of the last decade worldwide. That's no mean achievement. So, strategically, that was, again, I think a success, and each individual had to contribute his or her bit. So, Chris contributed in his way, Ray contributed in his way, Karl contributed in his way, I contributed in my way, and I'm sure the history of the FIL will be the history of a group of people. It's a bit like the Cavendish Laboratory, you know, or something like that.

I think the really great laboratory … just look at the … this is going to sound like hubris but look at the MRC Molecular Biology lab. Person after person of very high class who led that

laboratory, and the ethos and the productivity continued. And that was the model I had in my mind and I feel very proud that I was able to step down from power - from a powerful position - and have someone else take over. And we're already thinking about the person who's going to take over from Ray Dolan. It might be in five years time, but you know, and that's … you know, if you're going to keep energised, looking at new areas and so on, that's very important. Now, at the beginning, of course, looking at the breadth and making sure everything is going well and so on, it takes up a lot of your time. Yeah, I did that.

Alzheimer's Disease – delivery of oxygen to the brain

I set about trying to see what was the relationship between the delivery of oxygen to the brain and its use in normal people who were aged, in people who were suffering from so-called multi infarct dementia, where I expected there to be multiple dead areas, where the delivery of blood flow may be down but there was no tissue to use it up so that the ratio between the two would remain the same, or indeed, there would be too much blood flow, if anything. And senile dementia, as it was then called, which the hypotheses were - or the two hypotheses which were to be tested, was: 1) that there was not enough blood flow, and that the blood flow was dragging the metabolism down; and the other was that the brain was dying and the blood flow was just keeping up with what was left. And there were two important results. One was that where there were obvious infarcts, there yes … the blood flow was down but the metabolism was down as well, so it was matched. In the normals, the blood flow and metabolism were completely matched, and in the senile dements, they were also completely matched. So, there was no evidence for chronic ischemia at all; and secondly, the decrease in blood flow metabolism was regionally specific, and was down specifically over the parietal regions. Let me … let me just show you where those are. So, this is the brain - let me show it to you from the side, the front, the back, the top. These are the parietal lobes; these are the temporal lobes. This is the bit the boxer tries to hit so that the brain twists and the boxer falls unconscious. That's the top of the brain there - you can see the central fissure. That's the back, which is the bit you see with, and that's the frontal lobes. So, in the senile dements, the flow and metabolism remained matched, just as in normal people, but there was a marked decline in the flow and metabolism particularly in these areas here - the two parietal lobes - and then, when the disease got more intense and more severe - here in the frontal lobes - particularly on the lateral sides, here and here. And that pattern of decline of metabolism, which was reflecting the underlying degeneration, became the signature - the metabolic signature - for senile dementia and as we call it now, Alzheimer's disease.

Alzheimer's Disease – early detection: a clue from Huntington's disease

So, over the last seven or eight years, I've been concentrating particularly on using the study of the anatomy of the brain in order to try and complement what I'd found in those initial and late phases of Alzheimer's disease, with energy metabolism. You remember, there were those parts of the brain called the parietal lobes, here, and the frontal lobes later, which showed a very significant amount of loss of energy metabolism, suggesting a loss of function there and perhaps loss of neurons. There was always a paradox about that because the pathologists clearly showed us that inside the brain, here in the middle bits. So, if I take that off, you'll see here something called the hippocampus. It's called the hippocampus because it looks like a seahorse, which is very critical for memory, but that's where the first parts … and the cortex around the hippocampus, that's where the first problems arose in the pathology. So, why were we not seeing those problems in the function? And so, what I did was, when we began to start analysing images with these SPM routines - anatomical images - one of the first things we started to do was to begin to look at Alzheimer's disease. And lo and behold, we found that these early areas were showing atrophy, much earlier than the cortical areas, which were showing hypo-metabolism. So, the anatomical progression of structure seemed to mirror the pathological progression much better than the functional images, but the functional images gave us a much better analysis of what was going wrong with the brain.

The next phase was the issue of whether we could detect Alzheimer's disease before it became manifest, and that was a very important question because we knew from pathologists in another neurodegenerative disorder known as Parkinson's disease, that you needed to lose sixty per cent – seventy per cent of a specific set of neurons before you got your first symptoms. Now clearly, if you're a pharmacologist wishing to stop degeneration, if you start with sixty per cent or seventy per cent of neurons gone, you're pretty much on a hiding to nothing. But, consider if you could find a situation where only twenty per cent of the neurons have degenerated. In that situation, you have absolutely no symptoms. You still have a considerable amount of degeneration to go before you begin to get symptoms, and if you could just slow down the degeneration, as these are diseases of old age, you might be able to postpone the onset of symptoms beyond the average lifespan. Now, that would be a cure – a very peculiar notion of a cure. Not the sort of thing bacteriologists would consider a cure; the sort of thing people treating AIDS might consider a cure, but that's there postponing the onset. So, that became a really serious question, and it was difficult to see how to solve that problem, and then you hit on the idea that the thing to do would be to use a similar degenerative disorder, but where we had an external marker of whether the disease was going to occur or not. And we hit on this idea of studying Huntington's disease because

there, you can take a single blood sample, and depending on the genetic makeup of a particular gene on a particular chromosome, we can predict with a hundred per cent whether you're going to get the disease or not at some time in your life. I mean, if you live long enough. So, we took people - actually we took a set of scans that were done by neurologists who were experts in Huntingdon's disease in Tasmania, where there's an awful lot of this disease. We brought the scans over here and analysed them with our packages, and they were scans of thirty-six people, all of whom were normal, but we had their genotype as well, so we could divide them up into those with and without the mutation of the Huntington gene, and we could compare their scans. And we saw atrophy, and not only did we see an atrophy in those who *had* the mutation compared to those who didn't, but we also saw the atrophy specifically in those regions that the pathologists were going to point out when these people died and they examined their brains. So already, the caudate nucleus showed some atrophy, and other parts of the brain. So, that clearly showed us that there was an anatomical marker of the disease before it became manifest, and so that's proof of principle. We should be able to do that.

Alzheimer's Disease – another clue from schizophrenia

Now, the big difference between Alzheimer's Disease and Huntington's disease, is that one is monogenic (Huntingdon's Disease) - one gene - and the other is multi-genic - there are a lot of genes which will confer an increased risk. And again, it's difficult to know how to get at that, but we've done another proof of principle study in another multi-genic disorder, much less well understood, and that's schizophrenia. I have a colleague here at UCL, Hugh Gurling, who is a geneticist, and he's been really hunting for genes that will confer increased susceptibility, and there is one such gene that he's been particularly studying, which gives you an increased risk of about six to seven per cent of developing schizophrenia, if you have it.

So, we're able to compare the brains of normal people with those with schizophrenia, independent of whether they have the susceptibility gene or not. So, let me show you on the brain. Amongst other areas where there's local atrophy in schizophrenics, these parts of the cortex, the temporal poles, and also this under-part of what's the frontal lobe – we call this the orbito-frontal lobe because it sits immediately about the orbits of the eyes – there's focal atrophy there. There are other sites, but let's just think about those two sites. Now, when we come to look at the interaction, what we find is that in schizophrenics *with* the susceptibility gene, that atrophy is profound. In schizophrenics without the susceptibility gene, it's this atrophy that is profound. So, what we're doing is showing that using these techniques we can apportion the biological part of the susceptibility, if you like, through both the symptoms and

their brain basis. So, we think we've got an entrée there into beginning to examine these multi-genic disorders.

Alzheimer's Disease – technique for screening potential drug treatments

Now, finally in Alzheimer's Disease, we're aware of the fact that if we're going to treat Alzheimer's Disease, we're going to need to follow that treatment. We're aware that Alzheimer's Disease is a very long disease. We're aware that drug companies have vast numbers of potential drugs which they could use, and so we have a difficult problem because in order to get - using classical clinical trial techniques - a positive result on a potential drug, you're going to need lots of patients – possibly lots of patients of the same type – and you need to go to follow them for many years before you can say, 'Oh, well, this one's worth following up.' A disastrous situation economically and in all other ways, but imagine if you could take patients and you could, on the basis of their scan, stratify them according to severity - rather than using measures of behaviour - just how much of the brain has atrophied and where, and then take a small group, because what we deal with – our techniques are so sensitive, we just need dealing with ten, twenty, or thirty subjects – and then follow them in time with techniques which show change in the structure of the brain, with good sensitivity over periods of no more than three or six months. Potentially, you could screen vast numbers of drugs in that way, with these small cohorts examined with these morphometric techniques, structure techniques - what I've been calling VBM – over perhaps a year or two and get an indication of whether you needed to go to a clinical trial with this one or that one. Now, we've been doing that with VBM, actually, next door to this lab. Martin Rosser has been doing it with Nick Fox using other techniques, showing that you can detect really subtle changes in atrophy over periods of three to six months. We've done a collaborative study with them to show that we get the same results with our two techniques. The techniques are automated so that the person doing the scans or the analysis can't bias them. I think this is a very exciting area for translational medicine, and again, we now have the proof of principle.

Alzheimer's Disease – devising techniques for detecting early disease

And then, finally, the question of diagnosis. We've been using new techniques borrowed from computer science, essentially, where we've been trying to develop methods where we characterise the changes in scans of a particular disorder like Alzheimer's, even in a particular stage - perhaps early Alzheimer's or late Alzheimer's. And then taking scans – new scans – and asking the classifier to classify them as belonging or not belonging to that category. And because we didn't have a gold standard - of course, we were getting only eighty-five per cent accuracy, which incidentally is the accuracy that the clinician gets even if he does a full analysis, clinical analysis, with scans and everything else in the usual clinical

way. And so we did something really quite difficult, which is to get scans from people who had pathological verification of their pictures, and we got scans from Rochester in Minnesota, from here, and from all sorts of places where we had the scan, and we knew that the patient had the disease because they went on to post-mortem examination. And we had scans from normal people who we knew were normal because we also verified pathologically post-mortem that they had been normal and not had Alzheimer's. So, we had the absolute gold standard in both cases and we were able to distinguish Alzheimer's, early Alzheimer's, from new with ninety-five per cent accuracy, a hundred per cent sensitivity. Now, that is better than having a doctor do it.

Recovery from Stroke – two important discoveries

The biggest problem we had, wanting to look at how recovery occurs, is that when people have strokes, all the strokes are different size, shape, and in different places, and they affect all sorts of functions - sensation, action, cognition, and so on. So, being scientists, we needed to reduce this problem to try and grapple with it, and we knew that there was a particular set of young people who, when they had strokes, which affected the power in their limbs on the opposite side of the body from the bit of the brain, made remarkable recoveries over periods which were longer than a week but usually under six months to a year. So that we've all had the experience, as neurologists, to see a young person come in - certainly at the time when the Pills weren't safe - with young women come in who had a stroke deep in the motor part of the brain, profoundly paralysed down one side – three, four, six, twelve months later, functionally back to normal.

We thought, 'Well, now, if we want to look at what happens in the brain as it reorganises, we really need to be comparing those sorts of people who recover completely, with normal people because if they haven't recovered completely, the differences may be due to the fact that they're not functioning properly.' So, you know, the answer to the question, 'What has happened in the brain to cause recovery?' means that the recovery must be complete.

So, we found certain things which we could immediately generalise, and they were quite profound in the sense that we discovered that there were many more areas in the brain activated when you performed a movement with a recovered hand than when you performed exactly the same movement with a normal hand. Secondly, we discovered that those areas were distributed over both sides of the brain, even though usually one hand, making a simple movement like that, is controlled by the opposite side of the brain. So, those were two very important things. This was still all happening with PET but we were switching over to MRI

and we were finding very similar results with MRI, but at this stage again, a block. We found some facts but where do we go from here?

Recovery from Stroke – experiments on imagining and executing movements

So, what we needed was - it seemed to me - we needed a model where we could dispense with the behaviour, and that's when I began to think whether we … or try to think of a different model, and I began to explore the issue of thinking about the movements rather than doing them. And we did a series of experiments which were amongst the first, if not the first, to look at the whole issue of preparing to make a movement, imagining the movement, and executing the movement. And again, the results were quite stunning because all this folklore about pianists imagining their concerts while they're preparing for them, or tennis players imagining their backhanders in order to improve their function - absolutely true. If you imagine making this movement with your hand, you light up all the areas in the brain that are lit up by making the movement, except for the final area in the motor cortex which sends the signals out. It sends them out from here, which is the motor cortex, down through this part of the brain - the stem of the brain - out to the muscles. So, everything here was preparing you for the movement, but the final signal into the motor cortex, firing out to the muscles, was not there until you actually did the movement. There were very important parts here - the so-called dorsolateral prefrontal cortex. Great interest also to Chris Frith. They were very important in initiating action - free will, if you like. Chris starting talking about the physiology of free will, or perhaps some of us did, at any rate. Then there were these areas of the brain, the premotor cortex, which were involved in elaborating motor programmes for complex movements.

There was the motor cortex itself. There were parts in the parietal lobe, which we've already talked about, behind the motor cortex, that were involved in receiving information about how the movement was going ahead, and programming its parameters in space. All these components, together with other parts deep in the brain, the basal ganglia, parts of which we've already discussed in relation to Huntington's and Parkinson's disease - how this system within the brain worked, and that was an extremely exciting time. A lot of very basic physiology, if you like, a physiology which had not really been described before in relation to human behaviour, and it allowed us to start thinking biologically about things such as, how do you initiate an action? How do you attend to an action? Do you know that if you practice your backhand fantastically well so you've got a brilliant backhand, and then during the tennis match someone asks you to attend to your backhand, your game disintegrates. There are all sorts of fascinating behavioural quirks like that which began to be explained in terms of the physiology of the motor system.

Recovery from Stroke – how the brain remodels itself

We were able to initiate two major studies, one of which looked at individuals through time as they recovered, some of them scanned eight, ten times as they recovered. And the others - across a number of subjects - of different degrees of recovery. And here came the second major breakthrough, and that second major breakthrough was that, though in the initial phases of recovery, the whole motor system responds, in those who recover well – and this was completely counter-intuitive – all the excess activation comes back down to provide a small amount of activation, very similar to that which you get when you perform such a simple movement normally. Those who fail to recover well continued with this high level of activation, and our interpretation of that was that in those who can, with time, with more learning, with practice – whatever the other mechanisms one could think of – the system was able to narrow down back into a parsimonious set of nerve cells within the whole motor system, this little subset that dealt with this particular movement. In those who couldn't, there was no coming back so we now had an insight into the whole issue of how the brain remodels itself because this was a major remodelling exercise.

Visualising previously uncharted areas of the brain

So, both the Alzheimer's disease work, and the stroke work, started off paradoxically with pathophysiology in people who had disease, moved to a phase where one needed to understand the normal better, and have led, with methodological advances, to new approaches which are bringing us closer and closer to the sort of understanding and therapeutic strategies that might make a difference in the future. So, my view has always been that just producing a scanner is not going to solve anything. It's the use of that scanner that's going to be important. That is, I think, finally on the horizon, and I think not only these two areas that I've been working on, but other areas which have used the physiology of behaviour as their main basis, scanners as their methodologies, and thinking people designing good experiments as the way forward. It has been the right way and is the way we should continue to work.

I think that these various imaging techniques have completely transformed the science of psychology and neuropsychology, and how people who in the past had pencil and paper tests when they examined human behaviour, can go into the brain and investigate which bits of the brain are involved and why they're involved. And that spins off into new hypotheses and new ways of looking at things. Parts of the brain that were silent to neurologists - like the parietal lobes, the frontal lobes - we now have easy ways of examining them and examining

their functions and so on, so that's at the sort of basic science level, and a very big science for that matter.

The final thing I'd say is the history of these things - for MR is 1990; for PET is 1978. I think the changes in my lifetime have been extraordinary, and over another lifetime they will be even more extraordinary still, but what we certainly have are instruments for very carefully examining in space and time what is happening in the brain when we are carrying out our normal daily functions of thinking, perceiving and acting. So, I'm … no, I remain highly optimistic. I do not make exaggerated claims, and I believe that these measurements are complex and they need a lot of human thought input, as well as a lot of good machinery and a good mathematics and analytical capacity. But working together, I think there is still an enormous amount to be done with just what we have now.